REMARKS

In response to the Examiner's rejections, and in order to place the claims in condition for allowance, Applicant has amended claim 1. In addition to the advantageous inhibitory properties previously recited, amended claim 1 now recites an oligonucleotide "wherein said oligonucleotide consists of a nucleic acid sequence which is perfectly complementary to a contiguous sequence of 19 to 33 nucleotides in the region of VEGF beginning at nucleotide 259 and ending at nucleotide 293."[2] The numbering scheme used by Applicant refers to the VEGF-165 isoform. The amendment is fully supported by the specification and claims as originally filed. See, e.g., originally filed claims 2, 10 and 12; see also specification at Example 9, pages 23-25; Table 1 (page 24); Figure 14 in the specification (legend on page 10, lines 17-23). No new matter is added by the amendment, nor are any new issues of patentability raised by the amendment.

I. Rejections Under 35 U.S.C. § 102(e)

Claims 1, 9, 11, 13, 14, and 15 remain rejected as allegedly inherently anticipated by each of three U.S. patents granted to Robinson et al. [U.S. Pat. Nos.: 5,801,156; 5,710,136; and 5,814,620], or by the patent of Uchida et al. [U.S. Pat. No. 6,150,092]. See Office Action at 2-3. In response[3] to the Examiner's first Office Action, Applicant argued that the Examiner failed to provide a "basis in fact and/or technical reasoning to support the Examiner's determination that the allegedly inherent characteristics necessarily flow from the prior art." See Applicant's Nov. 18, 2002 Response at 2, citing *Ex Parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). The Examiner issued a Final Office Action, citing MPEP 2112.01 in support of the argument that a *prima facie* case of inherency had been made:

> "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the

[2] The numbering scheme referred to is described clearly in the specification at page 25, lines 1-5: "Nucleotide numbering shown in the fourth column [of Table 1] is from the translation start site of VEGF-165 isoform as published in Leung DW, Cachianes G, Kuang W-J, Goeddel DV, and Ferrara N. (1989) 'Vascular endothelial growth factor is a secreted angiogenic mitogen.' *Science* **246**:1306-1309."

[3] Applicant's first Response to an Office Action on the merits was filed November 18, 2002.

characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

See Office Action at 8. The Examiner also cites In re Spada, 911 F.2d 705, 709 (Fed. Cir. 1990) for the proposition that "products of identical chemical composition can not have mutually exclusive properties." See page 8. As an initial matter, Applicant notes (and the Examiner appears to agree) that none of the prior art oligonucleotide sequences cited by the Examiner are identical to the sequences that appear in Applicant's claims.

In response to the Examiner's rejections, and in order to place the claims in condition for allowance, Applicant has amended claim 1. In addition to the advantageous inhibitory properties previously recited, claim 1 now recites an oligonucleotide "wherein said oligonucleotide consists of a nucleic acid sequence which is perfectly complementary to a contiguous sequence of 19 to 33 nucleotides in the region of VEGF beginning at nucleotide 259 and ending at nucleotide 293."[4] The amendment is fully supported by the specification and claims as originally filed. No new matter is added by the amendment, nor are any new issues of patentability raised by the amendment.

The prior art cited by the Examiner fails to disclose an oligonucleotide which anticipates the composition of Applicant's amended claims because the prior does not disclose an oligonucleotide which reads on each limitation in Applicant's claims. See Gechter v. Davidson, 116 F.3d 1454, 1457 (Fed. Cir. 1997) ("Under 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim"). With respect to the Robinson patents, none of the patents disclose an oligonucleotide "perfectly complementary to a contiguous stretch of nucleotides in the region of VEGF beginning at nucleotide 259 and ending at nucleotide 293" as required by the claims.

The Uchida patent discloses three antisense oligonucleotide sequences of 19-33 bases in length which are complementary to the region of VEGF recited in the claims.[5] See Appendix A, attached to this Response. Each of these sequences [Uchida SEQ IDs Nos. 50, 51

[4] The numbering scheme referred to is described clearly in the specification at page 25, lines 1-5: "Nucleotide numbering shown in the fourth column [of Table 1] is from the translation start site of VEGF-165 isoform as published in Leung DW, Cachianes G, Kuang W-J, Goeddel DV, and Ferrara N. (1989) 'Vascular endothelial growth factor is a secreted angiogenic mitogen.' *Science* **246**:1306-1309."
[5] The Uchida patent utilizes its own numbering scheme based on Uchida's SEQ ID No. 1.

and 52] is 20 nucleotides in length. However, none of Uchida's oligonucleotides anticipate Applicant's amended claims because none of these sequences inhibits (1) the proliferation of cultured Kaposi's Sarcoma cells at an IC_{50} concentration of less than or equal to about 1.5 micromolar, or (2) the proliferation of cultured ovarian carcinoma cells at an IC_{50} concentration of less than or equal to about 2 micromolar, or (3) the proliferation of cultured melanoma cells at an IC_{50} concentration of less than or equal to about one micromolar, as recited in claims 1, 9 and 11, respectively.

The Examiner states that "it is assumed that the antisense [molecules] of Uchida et al inherently posses the ability to inhibit at the conditions recited in the claims without evidence to the contrary." See Office Action at 4. Clear evidence to the contrary is provided by a comparison of the data compiled in Appendix A. For instance, Uchida's SEQ ID No. 50 is *identical* to Applicant's SEQ ID No. 23. While Uchida's SEQ ID No. 50 was notable for its ability to reduce the expression levels of VEGF to "0%" in Uchida's in vitro assay[6], *the same oligonucleotide performed very poorly* in assays measuring its ability to inhibit the proliferation of Kaposi's sarcoma, melanoma or ovarian cancer cells. See Applicant's specification, Table 1, at page 24; see also Appendix A, attached.

Similarly, eighteen of 20 nucleotides in Uchida's SEQ ID No. 52 are shared with Applicant's SEQ ID No. 8. In spite of the fact that Applicant's SEQ ID No. 8 is 21 base pairs long, Applicant's SEQ ID No. 8 is the *least effective sequence assayed* in the claimed region in terms of its ability to inhibit proliferation of Kaposi's sarcoma, melanoma or ovarian cancer cells. See id. In contrast, Uchida et al. reports a "strong" inhibition of VEGF expression in Uchida's unique expression assays. See Uchida et al., column 20, lines 57-65 (defining a "strong inhibitory effect" as one that reduces the amount of expressed VEGF to a level between 10% and 30% that of untreated samples).

The evidence cited above shows the absence of any predictable correlation between Uchida et al.'s measurements of the inhibition of VEGF expression by oligonucleotides complementary to the claimed region of VEGF and the dramatic *inhibition of proliferation of particular cell types* achieved by the oligonucleotides claimed by Applicant. The evidence is sufficient to rebut the Examiner's presumption that any of the relevant oligonucleotides disclosed

in the patent of Uchida et al. *necessarily* have the anti-proliferative properties recited in Applicant's claims.[7] Applicant's claims are therefore not inherently anticipated because "[i]nherency may not be established by probabilities or possibilities." See re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999); see also Ex Parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

For the forgoing reasons, Applicant respectfully submits that the pending claims are not anticipated by any of the cited references, explicitly or inherently. Applicant respectfully requests withdrawal of the Examiner's rejection under 35 U.S.C. §102(e).

II. Rejections Under 35 U.S.C. § 103

A. Claims 1-3, 7-15 over Robinson (5,814,620; 5,710,136 and 5,801,156) and Uchida (6,150,092).

The Examiner rejected claims 1-3 and 7-15 as allegedly obvious under the Robinson patents (above) in view of the Uchida patent (above). The Examiner relies on the Robinson patents generally "to demonstrate that antisense oligonucleotides have been known for use in various methods of treatment prior to applicants invention . . . ." See Office Action at 4. The Examiner further alleges that (1) Uchida et al. "have taught methods of inhibiting VEGF with antisense oligonucleotides," that (2) Uchida et al. has disclosed a series of oligonucleotides which "target" a region of VEGF allegedly identical to that "targeted" by Applicant's oligonucleotides, and (3) that Applicant's specifically claimed oligonucleotides "either overlap, embrace, or are embraced" by the specifically claimed oligonucleotides recited in Uchida's claim 7. See id. at pp. 4-5. Finally, the Examiner argues that "[o]ne would expect that the inhibition conditions recited in the claims would be met since these values were observed upon making antisense targeted to the specific region clearly taught in the prior art." Id. at 5.

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[6] See Uchida et al US Pat. No. 6,150,092, column 12, Table I.

[7] Applicant refers the Examiner to the following reviews which are consistent with the observed difficulty of predicting, without testing, the efficacy of a particular antisense oligonucleotide sequence. See, e.g., Agrawal et al. "Antisense therapeutics: is it as simple as complementary base recognition?" Mol. Medicine Today (2000) Vol. 6, pp. 72-81; Jen et al. "Suppression of gene expression by targeted disruption of messenger RNA: available options and current strategies" Stem Cells (2000) Vol. 18, pp. 307-319; Crooke, S.T. "Progress in antisense technology: the end of the beginning" Methods in Enzymology (2000) Vol. 313, pp. 3-45.

As the Examiner's analysis suggests, an obviousness rejection requires (in addition to showing where all the elements of a claim are found in the prior art), a showing that one skilled in the art would have been motivated to combine the teachings in the cited references and that one skilled in the art would have had a reasonable expectation of success. See MPEP 2142, citing In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991). Furthermore, "the suggestion *and* the reasonable expectation of success must be founded in the prior art, *not in the applicant's disclosure.*" Id. (emphasis added).

Applicant has argued above that the limitations of the claims have not been shown to exist in the prior art. Specifically, neither the anti-proliferative effects of certain sequences *nor Applicant's sequences themselves* have been explicitly or inherently disclosed. In addition, the evidence also shows that Robinson et al. and Uchida et al. do not disclose enough information to allow one skilled in the art to reasonably expect that any antisense nucleotide sequence directed to the region explored by Applicant will have inhibitory properties.

As an initial matter, Applicant notes that the relationship between the oligonucleotides listed in Uchida's claim 7 and the oligonucleotides specifically claimed by Applicant has been inaccurately characterized. As shown in the attached Appendix, none of the antisense sequences listed in Uchida's claim 7 "embraces" any one of Applicant's claimed sequences. On the contrary, each of Applicant's claimed antisense sequences contains additional nucleotides not present in any particular oligonucleotide recited in Uchida's claim 7. Taken as a whole, Applicant's data strongly suggest that antisense oligonucleotides shorter than 19 nucleotides are not particularly effective at inhibiting proliferation of Kaposi's sarcoma, melanoma or ovarian cancer cells when targeted to the region of VEGF recited in the claims (compare, e.g., the unclaimed 18 nucleotide SEQ ID NO:24 with the 19 nucleotide SEQ ID NO: 21).

The Examiner's statement on page 5 of the Office Action that "the inhibition conditions[8] recited in the claims would be met since these values were observed upon making antisense targeted to the specific region clearly taught in the prior art" is legally irrelevant. The Federal Circuit has repeatedly warned that it is improper to simply use "that which the inventor

[8] Applicant assumes that the Examiner is referring to the inhibitory concentrations recited in the claims, and not the actual assay conditions used.

taught against its teacher." See W. L. Gore & Associates, 721 F.2d 1540, 1533 (Fed. Cir. 1983); see also Dembiczak, 175 F.3d at 999. Prior to Applicant's discovery, no one had characterized Applicant's claimed antisense oligonucleotides because *they did not previously exist.* The existence of a set of oligonucleotides with the properties shown in Applicant's specification could not have been predicted merely by knowing about Uchida's SEQ ID No. 7, nor could the utility of the sequences be determined merely by comparing them with allegedly similar sequences. The striking difference that a single oligonucleotide can make is evident from Uchida et al.'s own data, from Table I of Applicant's specification, and from the attached Appendix A (e.g., compare Applicant's SEQ ID NO:8 with Applicant's SEQ ID NO:9).

Uchida et al. did not show that *any* oligonucleotide targeted to certain regions of VEGF was reasonably *likely* to be useful. Rather, Uchida et al. showed only that certain regions of VEGF yielded a slightly greater percentage of useful antisense oligonucleotides than other regions. However, Uchida et al. also show that many oligonucleotides in these so-called "core" regions are inexplicably ineffective in Uchida et al.'s own assay. Taken together, the data suggests that the success of a particular oligonucleotide can not be reasonably expected upon examination of its sequence . See W. L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983) (prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention).

For example, within the 50 base region of VEGF depicted in the Appendix, over 400 unique complementary antisense oligonucleotides between 14 and 28 nucleotides in length may be constructed and tested. Uchida et al. tested 12 of these, and discovered that only half of them yielded "extremely strong" inhibitors of VEGF expression. *Uchida et al. also found that more than half of those sequences* (i.e., Uchida SEQ ID NOs: 51, 52, 139, and 151) *are surrounded by, or immediately adjacent to, ineffective or weak inhibitors of VEGF expression* (i.e., Uchida SEQ ID NOs: 53, 54, 140, 142 and 143) *as measured by Uchida et al.'s own assay.* This meager disclosure of a handful of useful sequences amidst a number of useless sequences and hundreds of unknowns surely falls far short of providing one skilled in the art with a reasonable expectation of success, particularly in light of the unpredictability of antisense technology at the time of Applicant's filing date (see references in footnote 7, infra). Applicant is not aware of any case law which sets a "magic number" of antisense sequence experiments

that is sufficient to provide a reasonable expectation of success, but expects that the sort of base pair by base pair "walk" in Applicant's specification is much closer to the mark than anything in Uchida or Robinson et al.

In summary, the references cited by the Examiner provide little guidance to those seeking to identify antisense oligonucleotides which target VEGF and have potent anti-proliferative activity in a variety of cancer cell types. See MPEP 2145.X.B., citing In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988) (no obviousness where prior art suggested only "a general approach that seemed to be a promising field of experimentation, [and] gave only general guidance as to the particular form of the claimed invention or how to achieve it."); see also In re May, 574 F.2d 1082 (no obviousness where evidence presented which showed no reasonable expectation that structural similar compounds would have similar properties). At best, Uchida et al. suggests only that one skilled in the art might *try* to find useful antisense oligonucleotides. Obviousness requires more. See In re O'Farrell at 903. For all the forgoing reasons, Applicant therefore respectfully requests withdrawal of the Examiner's rejection of claims 1-3 and 7-15 under 35 U.S.C. 103(a).

For all the forgoing reasons, Applicant respectfully requests withdrawal of the rejection of Claims 1-3 and 7-15 under 35 U.S.C. 103(a).

B. Claims 4-6; Robinson, Uchida, Barleon and Chan

The Examiner rejected claims 4-6 as allegedly unpatentable over the Robinson patents, in view of Uchida, and further in view of Barleon et al. and Chan et al. Barleon et al. is cited for teaching the use of an antiserum against VEGF and for observations relating to the role of flt-1 in the VEGF pathway. Chan et al is cited as teaching the roles of VEGF and its receptors "in various diseases." See Office Action at 6.

Claims 4-6 are indirectly dependent on claims 1 and 2 and therefore incorporate all of the limitations of claims 1 and 2. Neither Barleon or Chan address the deficiencies noted in Section IIA, above. If an independent claim is nonobvious . . . then any claim depending therefrom is nonobvious. See MPEP 2143.03, citing In re Fine, 837 F.2d 1071 (Fed. Cir. 1988).

Applicant therefore respectfully requests withdrawal of the Examiner's rejection of claims 4-6 under 35 U.S.C. 103(a).

CONCLUSION

In light of the forgoing Amendments and Remarks, withdrawal of the pending rejections and reconsideration of the claims is respectfully requested. A notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is respectfully requested to telephone Applicants' representative at (415) 393-2778.

NOTICE OF FIRM NAME CHANGE

Agent for Applicant wishes to inform the Office that the name of its firm has been changed to Bingham McCutchen LLP.

DATE: 4/7/03

Respectfully submitted,

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Legend to Appendix A

The sequence across the top and bottom of the alignment is a reference sequence complementary to Uchida et al.'s SEQ ID 7 (Uchida's SEQ ID 7 corresponds to nucleotides 242-284 of VEGF according to Applicant's numbering scheme).

The antisense oligonucleotides disclosed by Applicant and Uchida et al. are aligned between this top and bottom reference sequence. Uchida et al.'s sequences are shown in plain red (in the color copy) and his SEQ ID NOs are *italicized*. Applicant's claimed sequences are shown in plain (green) text and Applicants claimed SEQ ID NOs are in **bold font**. Applicants unclaimed sequences are shown in plain (black) text and the SEQ ID NOs are also in plain text.

Uchida et al.'s expression data (from Uchida et al.'s Tables 1 and 2) are presented in parentheses to the right of Uchida et al.s corresponding SEQ ID Nos. Note that Uchida et al. disclose both oligonucleotides which are either 20 or 14 nucleotides in length. The data for the 14 nucleotide sequences is presented in a column to the right of the data for the 20 nucleotide oligos.

Applicant's measurements of IC_{50}s (from Table 1 in the Applicant's specification, page 26) are shown in columns to the right of Applicant's corresponding SEQ ID NOs for Kaposi's Sarcoma cells (IC_{50}**KS**), ovarian cancer cells (IC_{50}**OV**) and melanoma cells (IC_{50}**MEL**).

APPENDIX A: COMPILATION OF ANTISENSE SEQUENCE DATA (legend on following page)

5′ GG ATGGCTTGAA GATGTACTCG ATCTCATCAG GGTACTGCCTG 3′ (complement of Uchida SEQ ID 7)

	SEQ ID #		IC_{50}KS	IC_{50}OV	IC_{50}MEL
CATCGCATCAGGGGCACACA	*Uchida 54*	*(51%)*			
TCGGATCAGGGGCACACAGG A	6		10	>10	>10
ATCAGGGGCACACAGG ATGG	*Uchida 53*	*(23%)*			
CAGGGGCACACAGG ATGGCT	7		>10	>10	>10
GGGGCACACAGG AT	*Uchida 143*	*(51%)*			
GGGCACACAGG ATGGCTTGAA GATGTACTCG AT	**28**		0.6	1.2	1.3
GGGCACACAGG ATGGCTTGAA GA	**29**		0.7	1.5	1.2
GGCACACAGG ATGGCTTGAA	*Uchida 52*	*(11%)*			
GGCACACAGG ATGG	*Uchida 142*	*(38%)*			
CACACAGG ATGGCTTGAA GAT	8		8.2	>10	>10
CACACAGG ATGGCT	*Uchida 141*	*(9%)*			
ACACAGG ATGGCTTGAA GATG	**9**		0.85	1.6	1.6
CACAGG ATGGCTTGAA GATGT	**10**		0.9	1.9	1.5
CACAGG ATGGCTTG	*Uchida 140*	*(21%)*			
ACAGG ATGGCTTGAA GATGTA	**11**		1.6	3.4	2.7
CAGG ATGGCTTGAA GATGTAC	**12**		0.9	1.8	0.9
CAGG ATGGCTTGAA GATGTA	*Uchida 51*	*(4%)*			
CAGG ATGGCTTGAA	*Uchida 139*	*(4%)*			
AGG ATGGCTTGAA GATGTACT	**13**		0.4	1.1	0.6
GG ATGGCTTGAA GATGTATTC	**14**		0.38	1.1	0.7
GG ATGGCTTGAA GATGTACT	**20**		0.95	2.7	1.0
GG ATGGCTTGAA GATGTAC	**21**		1.1	2.8	1.4
GG ATGGCTTGAA GATGTA	22		3.8	>10	5.8
G ATGGCTTGAA GATGTACTCG	**15**		1.11	2.4	1.2
ATGGCTTGAA GATGTACTCG A	**16**		1.42	3.0	2.5
ATGGCTTGAA GATG	*Uchida 138*	*(3%)*			
TGGCTTGAA GATGTACTCG AT	2		2.1	5.2	3.2
TGGCTTGAA GATGTACTCG A	26		3.4	>10	4.7
GGCTTGAA GATGTACTCG ATC	**17**		0.5	1.2	0.5
GGCTTGAA GATGTACTCG AT	23		4.8	>10	7.1
GGCTTGAA GATGTACTCG AT	*Uchida 50*	*(0%)*			
GCTTGAA GATGTACTCG AT	24		4.6	>10	6.2
GCTTGAA GATGTACTCG ATCT	**18**		1.38	3.1	2.2
CTTGAA GATGTACTCG ATCTC	19		2.42	6.0	3.7
CTTGAA GATGTACTCG AT	25		6.2	>10	8.6
AA GATGTACTCG ATCTCATC	*Uchida 49*	*(0%)*			

5′ GG ATGGCTTGAA GATGTACTCG ATCTCATCAG GGTACTGCCTG 3′ (*antisense* to Uchida SEQ ID 7)